REMARKS

The present invention relates to regulatory T cells (Treg cells) and methods of long-term, culture-expanding, activating and using same in immunotherapy and for the suppression of autoimmune responses.

By way of the present Amendment, claims 6 and 12-27 have been canceled, and claims 1-5, 7-11, and 28-29 have been amended. In addition, new claims 30-35 have been added. No new matter has been added by way of these amendments.

Claim 1 has been amended to at least incorporate the limitations of claim 27. Claim 27 was not rejected as being anticipated or obvious over the cited art. A more detailed discussion of the amendments to the claims is set forth below.

Applicants appreciate the time taken by the Examiner during the telephone interview that took place on September 6, 2007, with Applicants' representative, Kathryn Doyle (the undersigned). During the telephone interview, Applicants agreed to amend the claims to clarity the purification process.

This Amendment serves to address the Advisory Action dated October 15, 2007 and the Final Office Action dated April 10, 2007. Specifically, the Advisory Action indicated that the Amendment filed September 18, 2007 will not be entered. Accordingly, the present Amendment is being filed concomitantly with an RCE.

New Claims

Claims 30-35 have been added herein. Support for claims 30-35 is found throughout the specification and therefore do not constitute new matter.

Specifically, support for anti-CD25 antibody conjugated to a magnetic bead as set forth in claim 30 and dependent claims therefrom is at least found in paragraph [0185] page 51 where a conjugated anti-CD25 magnetic microbead is disclosed.

Support for a secondary agent as set forth in claims 31 and dependent claims therefrom is at least found in paragraph [0091] on page 27 where a two step purification protocol is disclosed to encompass the use of a secondary agent (e.g., anti-FITC). Support for an "indirect" method in claim 31 and dependent claims therefrom is at least found in paragraph [186] on page 52.

Support for claim 32 relating to a high level of stringency is at least found in paragraph [0087] on page 26 where a high level of stringency technique is described.

Support for claims 33 and 34 is at least found throughout the specification and in the original filed claims 3 and 4, respectively.

Support for claim 35 is at least found in paragraph [0091] on page 27.

Accordingly, no new matter has been added by way of these amendments.

Objection to claim 28

The Examiner has objected to claim 28 because the word "ratio" appears to have been omitted.

In response, claim 28 has been amended to state that "the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is at least 1:5".

Response to Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-11 and 27-29 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting the phrases "using a lower titer of anti-CD25" and "modified magnetic antibody cell sorting". The Examiner contends that the metes and bounds of "lower titer" is not clear and that the skilled artisan would not know how the "modified magnetic antibody cell sorting" procedure is modified.

In response, Applicants have amended claim 1 to remove the recitation of "a lower titer" and the word "modified". In addition, claim 1 has been amended for clarity purposes as discussed more fully below. Applicants respectfully submit that the amendments to the claims places the claims in compliance with the standard set forth in 35 U.S.C. 112, second paragraph.

Claim 1 has been amended to indicate that the method comprises a step of isolating cells that bind anti-CD25 antibody from a sample of human $CD4^+$ T cells. More specifically, the method includes isolating cells using a double column magnetic antibody cell sorting (MACS) purification procedure. Support for this amendment is found throughout the specification and in the original claims.

For example, Example 8 discloses that $CD25^+$ were isolated by positive selection from peripheral blood mononuclear cells (PBMC) using anti-CD25 magnetic microbeads and purified over a magnetic column. The cells were then applied to a second magnetic column,

washed, and re-eluted. After the double column procedure (*e.g.*, application of the cells to a second magnetic column), cells were routinely >93% pure (for CD25) by FACS analysis.

Claim 1 has also been amended to indicate that the method includes a culture-expansion step. More specifically, the culture-expansion step comprises contacting isolated $CD4^+CD25^+$ Treg cells with immobilized anti-CD3 antibody and immobilized anti-CD28 antibody at a predetermined ratio, whereby the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is less than 1.

Support for the phrase "immobilized" with respect to the anti-CD3 and anti-CD28 antibodies can be found in the descriptions for Figures 3 and 11 as well as in Example 3.

With respect to the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is less than 1, support for a ratio of less than 1 is found throughout the specification, for example, paragraph 86 beginning on page 25. The present invention is based partly on the fact that when various ratios of anti-CD3 to anti-CD28 were tested (20:1, 5:1, 1:1, 1:5, 1:20, respectively) on the microbeads. It was observed that the higher ratio of anti-CD28 beads induced selective outgrowth of suppressor T cells. More specifically, the ratio of 1:5 and 1:20 anti-CD3/anti-CD28 beads generated cell lines that were less contaminated with non-suppressor T cells.

Accordingly, Applicants respectfully request that the rejection of claims 1-11 and 27-29 under 35 U.S.C. § 112, second paragraph, as being indefinite be reconsidered and withdrawn. Furthermore, Applicants contend that claim 1 and dependent claims therefrom fully comply with the standards set forth under 35 U.S.C. § 112, second paragraph.

Rejection of claims 1-4, 11 and 26 pursuant to 35 U.S.C. §102(e), or in the alternative pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 1-4, 11 and 26 under 35 U.S.C. § 102(e) as being anticipated by Schuler et al. (U.S. Patent Application Pub. No. 2005/0101012) as evidenced by the CD25 MicroBeads magnetic cell sorting protocol and the CD8 Microbead online product literature, or in the alternative, under 35 U.S.C. §103(a) as obvious over Schuler in view of the MicroBead magnetic cell sorting protocols.

Solely in order to expedite prosecution of the present application, Applicants have canceled independent claim 26 and have amended claim 1 to incorporate the limitation of claim

27, which was not rejected as being anticipated or obvious over Schuler et al. in view of the CD25 MicroBead protocol.

Specifically, amended claim 1 recites that the culture-expanding step includes contacting an isolated population of human $CD4^+CD25^+$ Treg cells with "immobilized anti-CD3 antibody and immobilized anti-CD28 antibody at a predetermined ratio, wherein the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is less than 1."

In view of this amendment, Applicants respectfully submit that claim 1 is not anticipated or rendered obvious by Schuler et al. in view of the cited MicroBeads magnetic cell sorting protocols. Withdrawal of this rejection is thus respectfully requested.

Rejection of claims 1-3, 5, 11 and 29 pursuant to 35 U.S.C. §102(e), or in the alternative pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 5, 11, and 29 under 35 U.S.C. § 102(e) as being anticipated by Roncarolo et al. (US2004/0173778), or in the alternative, under 35 U.S.C. 103(a) as obvious over Roncarolo in view of the CD25 MicroBead protocol.

As indicated above, solely to expedite prosecution of the present application, Applicants have amended claim 1 to incorporate the limitation of claim 27, which was not rejected as being anticipated or obvious over Roncarolo et al. in view of the CD25 MicroBead protocol.

Specifically, amended claim 1 recites that the culture-expanding step includes contacting an isolated population of human $CD4^+CD25^+$ Treg cells with "immobilized anti-CD3 antibody and immobilized anti-CD28 antibody at a predetermined ratio, wherein the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is less than 1."

In view of this amendment, Applicants respectfully submit that claim 1is not anticipated or rendered obvious by Roncarolo et al. in view of the cited MicroBead magnetic cell sorting protocols. Withdrawal of this rejection is thus respectfully requested.

Rejection of claims 6-10 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 6-10 under 35 U.S.C. § 103(a) as being unpatentable over Roncarolo et al. in view of Diehn et al., (2002, PNAS 99:11796-11801).

As indicated above, solely to expedite prosecution of the present application, Applicants have amended claim 1 to incorporate the limitation of claim 27, which was not rejected as being obvious over Roncarolo et al. in view of Diehn et al.

Specifically, amended claim 1 recites that the culture-expanding step includes contacting an isolated population of human $CD4^+CD25^+$ Treg cells with "immobilized anti-CD3 antibody and immobilized anti-CD28 antibody at a predetermined ratio, wherein the ratio of the amount of anti-CD3 antibody to anti-CD28 antibody is less than 1."

In view of this amendment, Applicants respectfully submit that claim 1 is not anticipated or rendered obvious by Roncarolo et al. in view of Diehn et al. Withdrawal of this rejection is thus respectfully requested.

Rejection of claim 1 for Nonstatutory Obviousness-type Double Patenting

The Examiner has provisionally rejected claim 1 under 35 U.S.C. §101 on the grounds of nonstatutory obviousness-type double patenting. The Examiner is of the opinion that claim 1 is unpatentable over claims 1-3, 10 and 14 of copending Application No. 11/226,168.

Applicants thank the Examiner for placing this rejection in abeyance until claims have actually issued or are deemed allowable in this application or copending Application No. 11/226,168.

Summary

Applicant respectfully submits that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that the claims are now in condition for allowance. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

BRUCE BLAZAR ET AL.,

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(Date)

By: _____

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